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Review

Nimodipine prophylaxis in aneurysmal subarachnoid hemorrhage, a question of tradition or evidence: A scoping review

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ABSTRACT

Background: The prophylactic use of nimodipine following subarachnoid hemorrhage is a practice established four decades ago when clinical management differed from current and the concept of Delayed Cerebral Ischemia (DCI) was not established. The applicability of the original studies is limited by the fact of not reflecting current practice; by utilising a dichotomised outcome measure such as *good neurological outcome* versus *death and vegetative state*; by applying variable dosing regimens and including all causes of poor neurological outcome different than DCI. This study aims to review the available evidence to discuss the ongoing role of nimodipine in contemporaneous clinical practice.

Methods: PRISMA guidelines based review, evaluated the evidence on the prophylactic use of nimodipine. The following search engines: Medline, Embase, Cochrane, Web of Science and PubMed, identified Randomized Control Trials (RCTs) with neurological benefit as outcome measure and the impact of fixed versus weight-based nimodipine dosing regimens.

Results: Eight RCT were selected. Three of those trials with a total of 349 patients, showed a reduction on death and vegetative state (pooled RR: 0.62; 95 % confidence interval-CI: 0.45, 0.86) related to DCI. Amongst all studies, all cause death (pooled RR = 0.73, [95 % CI: 0.56, 0.97]) favoured a fixed-dose regimen (pooled RR: 0.60; [95 % CI: 0.43, 0.85]).

Conclusion: Available evidence demonstrates that nimodipine only reduces the risk for DCI-related death or vegetative state and that fixed-dose regimens favour all cause infarct and death independent of DCI. Contemporaneous studies assessing the benefit of nimodipine beyond death or vegetative states and applying individualized dosing are warranted.

1. Introduction

Subarachnoid hemorrhage (SAH) is a leading cause of neurological morbidity and Years-Of-Life-Lost [1,2]. Patients frequently require intensive care unit (ICU) admission, prolonged hospital stay and rehabilitation leading to significant impact on resources [3,4]. Furthermore, its detrimental effect on cognitive and psychological functions limits patients' return to the community [5,6]. Although angiographic vasospasm led Delayed Cerebral Ischemia (DCI) remains an important cause of stroke and poor neurological outcome after SAH, multiple other pathophysiological processes independent of angiographic vasospasm have been attributed to DCI [7]. According to expert consensus DCI and

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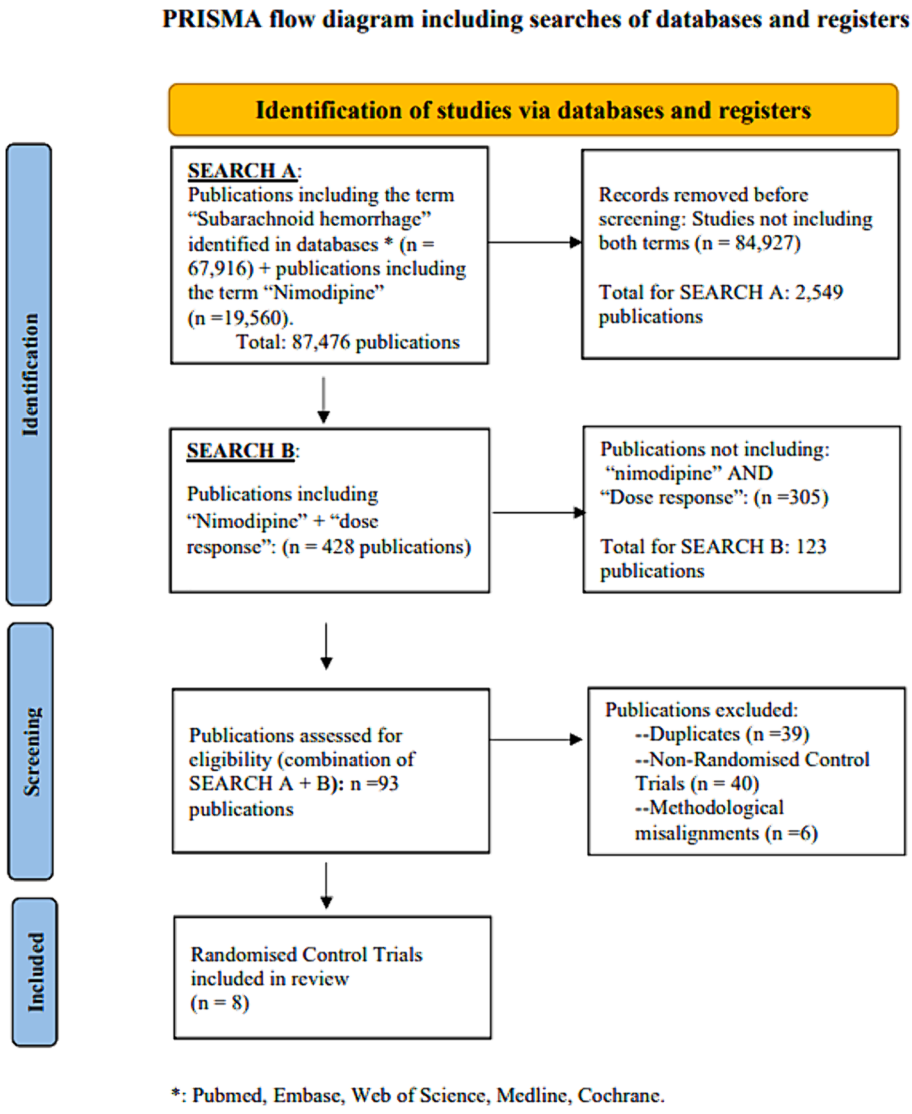
PRISMA flow diagram including searches of databases and registers
Identification of studies via databases and registers
Identification
SEARCH A:
Publications including the term "Subarachnoid hemorrhage" identified in databases * (n = 67,916) + publications including the term "Nimodipine" (n =19,560).
Total: 87,476 publications
Records removed before screening: Studies not including both terms (n = 84,927)
Total for SEARCH A: 2,549 publications
SEARCH B:
Publications including "Nimodipine" + "dose response": (n = 428 publications)
Publications not including: "nimodipine" AND "Dose response": (n =305)
Total for SEARCH B: 123 publications
Screening
Publications assessed for eligibility (combination of SEARCH A + B): n =93 publications
Publications excluded:
--Duplicates (n =39)
--Non-Randomised Control Trials (n = 40)
--Methodological misalignments (n =6)
Included
Randomised Control Trials included in review (n = 8)
*: Pubmed, Embase, Web of Science, Medline, Cochrane.

Fig. 1. Flowchart of search by terms. Combination of search strategy concluding on the selected RCTs.

cerebral infarct must be reported independently of angiographic vasospasm [7] with the terminology of "vasospasm" reserved for angiographic arterial narrowing only and the terminology "symptomatic vasospasm" becoming an obsolence. However those distinctions were not considered during the design of the trials that set up the evidence for nimodipine. DCI is multifactorial and includes: cerebral arterial microthrombosis [8], cerebral autoregulatory dysfunction, abnormal collateral flow dynamics [9] and cortical spread depolarization [10]. These processes lead to perfusion mistmatch and decoupling of energy; mechanisms independent of the effects of nimodipine and similarly, not well understood at the time when the evidence for nimodipine was established. Therefore, the possibility that in these situations, angiographic vasospasm could have been an epiphenomena as opposed to the direct cause for poor outcome, adds uncertainty tothe role of nimodipine.

There are substantial differences between current clinical practice and when the original Randomized Control Trials (RCTs) were conducted. At that time, the management of patients with SAH did not prioritise the securement of the aneurysm in the acute phase. Such scenario would subject patients to a situation where neuroimflamation would compound an ischemic milieu, hypothetically increasing the cellular inflow of calcium [11,12], a therapeutic target for nimodupine. This situation contrasts with contemporaneous practice. Furthermore, current management is based upon the RCTs that established the use of nimodipine as prophylaxis of angiographic vasospasm [13–19]. These studies have been systematically reviewed [20–23] but their methodology differs from today's standards. An outstanding difference is found on their samples' size as they were not statistically powered for outcome difference. In addition, previous studies utilized dichotomous scales such as *poor outcome* defined as death and vegetative state versus *good outcome* which included an outcome of severe disability. But the use of those dichotomised measures may have overestimated the effect of nimodipine. Furthermore, in the majority of these studies the presence of angiographic vasospasm as a cause of neurological deficit or cerebral infarct was not confirmed. Instead, neurological deficits of all causes such as hemorrhage, hydrocephalus and other complications independent of cerebral ischemia were included, leading to the posibility of overstating the benefit of nimodipine.

Despite the novel developments in the field of neuro-interventional radiology [24–26], the overall outcome following SAH is clouded by its morbidity and high mortality. SAH patients benefit of the advanced management of its complications, but minimal progress has occurred in the field of prevention. Nimodipine remains the only preventative strategy aiming to improve neurological outcomes, but its mechanism of action remains unclear, its use is increasingly questioned [27–30] and evolving interest focuses on the approach to dosing. The standard dosing

Table 1
RCT's focusing on the prophylactic use of nimodipine.

Author Journal Year	Study type Participants	Intervention	Outcome measure	Definition of vasospasm	Study endpoint	Main finding
Allen G S NEJM 1983	Multicentre (5-university hospitals) Total patients: 125	0.7 mg/K Maintenance: 0.35 mg/kg/4h x 21 days versus Gelatin capsules containing placebo	**Clinical deficit related to CVS.** Clinical severity including death until 21d after bleed.	+ **Confirmation of CVS by angiography**	Clinical scale * applied at 21 days from bleed: "Normal" "Mild or moderate" "Severe": Eye response 1–2 Verbal response: 1–2 Motor response: M1-4 months.	=**1 severe disability** within nimodipine group versus **8 severe disabilities** in the placebo group
Ohman, J JNeurosurg 1988	Single centre Total patients: 213 *Exclusion criteria: Patients with renal or liver disease.	Group A (104n): Loading dose: 0.25pcg/kg/min x 2 h followed by: 0.5pcg/kg/min x 7–10 days followed by 360 mg/day up to 21d Group B (109n): Placebo		Angiography for the confirmation of CVS not performed regularly.	Applied a clinical scale of 3 categories: Independent Dependant Death	=**1 death** within nimodipine group versus **9 deaths** in the placebo group
Philippon, J Acta Neurochir. 1986	Single centre Total patients: 70	mg/4h x 21 days. *Versus* Placebo	**Clinical deficit related to CVS.**	+ **Confirmation of CVS by angiography** Radiological scale for the severity of radiological CVS: Moderate < 50 % vessel calibre reduction Severe > 50 % calibre reduction	days from bleed	**severe disability** related to CVS: =Severe disability: **2** patients in the nimodipine group versus **10** patients in the placebo group
Petruk, K JNeurosurg 1988	Multicentre (17-university hospitals) Total patients:154* Only recruited poor clinical grades SAH	Group A (73n): Enteral nimodipine: 90 mg/4h x 21d Group B (83n): Placebo	**Clinical deficit related to CVS.** Clinical severity including death until 21d after bleed.	**Confirmation of CVS by angiography** Radiological scale for the severity of radiological CVS: Severe > 50 % lumen narrowing Moderate 30–50 % lumen Mild < 10 % narrowing Local distribution versus diffuse	months	**severe disability** related to CVS: =Severe disability: **10** patients in the nimodipine group versus **22** patients in the placebo group
Pickard JD BMJ 1989 *"THE BRANT Study"*	**RCT** Multicentre (4 centres in UK) Total patients:554	Group A (278n): Enteral nimodipine: 60 mg/4h x 21 days. *Versus* Group B (276n): Placebo		Angiography for the confirmation of CVS not performed regularly.	months Applied a clinical scale of 3 categories: "Good outcome": none–mild- moderate disability"Bad outcome": Severe disability or death	**clinical deficits** attributed (not confirmed) to CVS: =Cerebral **infarct**: **39** patients in the nimodipine group versus **61** patients in the placebo group =Death **43** patients nimodipine group versus **60** in the placebo group =Severe disability: **12** patients in the nimodipine group versus **31** patients in the placebo group
Ohman J JNeurosurg 1991	Placebo-control Single centre Total patients: 265** Renal or liver disease was an exclusion	Group A (104n): Infusion nimodipine x 10 days followed by oral to 21d Group B (161n): Placebo		Radiological scale for the severity of radiological CVS when performed: Severe > 50 % lumen narrowing Moderate 30–50 % lumen None or mild if < 10 % narrowing	——3 years	**clinical deficits** attributed (not confirmed) to CVS: =**13** patients within nimodipine group versus **38** patients in the placebo group.
Ohman J JNeurosurg 1991	Single centre Total patients: 213	x 7–10 days followed by 60 mg/4h/Oral up to 21d *Versus* Placebo	Cerebral infarct Death		——3 years + CT to exclude stroke	**34 cerebral** infarcts within nimodipine group versus **49 infarcts** in the placebo group

(*continued on next page*)

Table 1 (*continued*)

Author Journal Year	Study type Participants	Intervention	Outcome measure	Definition of vasospasm	Study endpoint	Main finding
Neil Dwyer Eur Heart 1987	Single centre Total patients:75	mg/4h x 21 days *Versus* Placebo	"Good" outcome "Bad" outcomeDeath	intended.	months	n: **1 death** within nimodipine group versus **6 deaths** in the placebo group

CVS: Cerebral vasospasm; * clinical scale based on the Glasgow Coma Scale; SAH: Subarachnoid Hemorrhage; GOS: Glasgow Outcome Score.

of nimodipine contrasts with expanding concepts such as individualized management and precision medicine. Whilst initial studies used weight-adjusted dosing [13–15], fixed dosing regimens became the standard of practice [16–19]. However, using a universal dose of nimodipine, may lead to suboptimal effects due to its variability in absorption and its idiosyncratic dose–effect. This situation could favour suboptimal concentrations of nimodipine at the Pial arteries and the subarachnoid space, the anatomical site related to the genesis of cerebral vasospasm [31]. Similarly, using a universal dose of nimodipine may lead to overdosing in vulnerable populations, increasing the likelihood of side effects.

In this scoping review, the authors have analysed the evidence of nimodipine based on the original studies' endpoints. We have isolated the studies that tested the capacity of nimodipine to reduce angiographic vasospasm related DCI from those who reported an outcome benefit of any cause. The rational for this approach is to increase specificity and accuracy when referring to nimodipine as mainstain prophylaxis, exploring further research in the field of prevention. Also, in this review the authors have analysed the evidence of nimodipine based on the dose used on the original trials with the intention to identify knowledge gaps, discuss future pathways for improvement and inform further studies.

2. Materials and methods

This review aligned to the Joanna-Briggs Institute recommendations and the Preferred Items for Systematic Review and Meta-analysis (PRISMA) guidelines [32]. A completed PRISMA checklist can be found as Supplementary Materials.

2.1. Search strategy

Pubmed, EMBASE, Web of Science and Cochrane, through the library tools of the University of Queensland were searched, with no initial search restrictions. The search comprised different stages: an initial Medline search identified relevant keywords; this was followed by the use of keywords to conduct further literature search; reference lists were then collected from included articles and key author searches were completed. Three database searches with superimposed filters and criteria were combined and duplicates were removed. The search covered the following terms: "subarachnoid hemorrhage", "subarachnoid haemorrhage", "nimodipine" *OR* "calcium channel blockers", "dose response" *OR* "dose response relationship" including Medical Subject Headings (MeSH) terms. A combination of these terms-search was implemented using the Boolean operators of: "AND" (to combine "subarachnoid hemorrhage", "subarachnoid haemorrhage" with "nimodipine"), "OR" (when referring to "nimodipine" OR "calcium channel blockers" as well as "dose response" OR "dose response relationship"). We also conducted an extensive literature search from the wider topic of *subarachnoid hemorrhage* to the narrower search of the *dose response of nimodipine* using additional filters and advanced searches. Our intention was to achieve the most specific but also thorough data search to ensure that all relevant studies, were included. Because this was a very focused topic with a-priori expectations of finding only few randomized trials, we included pharmacokinetic studies and non-randomized studies to avoid missed information, but the final selection only included RCTs.

This scoping review was registered at the PROSPERO international prospective register: PROSPERO registration number CRD42020188319, initially as a systematic review to allow for the search and thoroughness of the analysis related to systematic reviews; but it was later re-edited as a scoping review for the purpose of this manuscript and following editorial recommendations.

2.2. Selection criteria

2.2.1. Population

The sample of interest included adults admitted to a tertiary ICU with the diagnosis of aneurysmal SAH of any grade and defined by the presence of subarachnoid blood in the subarachnoid space with or without a demonstrated aneurysm on cerebral computerized tomography angiography (CTA). It also included patients with a normal computerized tomography (CT) but a positive xanthochromia index on cerebral-spinal fluid (CSF) and with or without demonstrated aneurysm. Patients with *peri*-mesencephalic SAH were also included.

2.2.2. Types of outcome measure

Primary outcome measure: Clinical outcome benefit, defined as a reduction in DCI events *only* related to angiographic vasospasm confirmed by CTA or Digital Subtracted Angiography (DSA).

Second outcome measure: Clinical outcome benefit, defined as a reduction on the incidence of cerebral infarcts, diagnosed via CT *only* related to cerebral vasospasm and confirmed by CTA or DSA.

Third outcome measure: Clinical outcome benefit, defined as a reduction on neurological deficits and cerebral infarcts of *all* causes between two different nimodipine prescription regimens (a fixed and a weight-based regimen).

2.2.3. Study records, data management and selection process

Two investigators (JP and JB) independently screened the selected abstracts to identify studies that focused on: dosing of nimodipine in SAH; pharmacokinetic and pharmacodynamic (PK/PD) data; dose–response to nimodipine; pathway of administration (enteral or parenteral); nimodipine concentrations in plasma and / or in CSF; presence of a "neuro-worsening" (defined as a decrease of 2 or more points on the motor score of the Glasgow Coma Scale (GCS), a new-onset lack of pupillary reactivity or the development of pupillary asymmetry of 2 or more mm from baseline or new CT changes); mortality and neurological outcomes secondary to cerebral vasospasm related DCI.

2.2.4. Data extraction

Data was extracted in duplicates by two reviewers (JP and JB) using a standardized data extraction tool. When required, input from a senior librarian enabled the search to have maximal robustness. Both reviewers read all selected studies independently and completed a Chalmers scoring sheet that had been designed for the purpose of extracting data homogeneously across all studies. The data extracted was based on: year and language of publication; country where studies were performed; type of study and patient enrollment (consecutive or non-consecutive). Primary outcome data: DCI events *only* related to angiographic vasospasm. Secondary outcome data: cerebral infarction related to confirmed angiographic vasospasm and neurological deficits of all

Table 2
Neurological deficits with confirmed cerebral vasospasm.

Author	Drug No vasospasmNo neurological deficit	Drug No vasospasmwith neurological deficit	Drug vasospasmNo neurological deficit	**Drug vasospasm with neurological deficit**	Drug vasospasm withDeath	Placebo No vasospasmNo neurological deficit	Placebo No vasospasmwith neurological deficit	Placebo vasospasmNo neurological deficit	**Placebo vasospasm with neurological deficit**	Placebo vasospasm withDeath
Allen GS ('83)	24n / 56 (Total subjects on drug: 56n)	19n / 56	8n / 56	**4n / 56**	1n / 56	28n / 60 (Total subjects on placebo: 60n)	16n / 60	6n / 60	**7n / 60**	3n / 60
Philippon ('86)	Not disclosed (Total subjects on drug: 31n)	11n / 31	Not disclosed	**10n / 31**	2n / 31	Not disclosed (Total subjects on drug: 39n)	12n / 39	2n / 39	**14n / 39**	4n / 39
Petruk K ('88)	39n / 72 (Total subjects on drug:72n)	7n / 72	Not disclosed	**26n / 72**	Not disclosed	28n / 82n (Total subjects on drug: 82n)	8n / 82	Not disclosed	**46n / 82**	Not disclosed

causes amongst groups with different nimodipine prescription-regimen (fixed-dose compared to weight-based dose).

2.2.5. Types of studies

Only RCTs were included. Studies published from January 1, 1980 to current date and publications written in English. The following were excluded: Non-randomised, retrospective cohort and didactic (editorial) studies; experimental or animal models; publications prior to the inclusive date; studies only focusing on radiological response to nimodipine (specifically those using intraarterial nimodipine for the treatment of established angiographic vasospasm); studies based on general management of SAH as opposed to focused dose–effect of nimodipine; trials with historical controls and dose-finding studies not including a placebo-control group.

2.2.6. Quality assessment and risk of bias in individual studies

The two investigators (JP and JB) independently assessed the risk for bias within the selected studies applying the Chalmers scale [33]. Only those selected studies for which both investigators agreed in the accomplishment of all selection criteria were included in the final review. The quality of each selected RCT was appraised using the Chalmers scale aligned with the Cochrane collaboration tool recommendations for the assessment of bias in RCT [34], results provided in the appendixes.

2.2.7. Data synthesis

Studies were grouped by study design (randomized); location (single or multicenter); endpoints; outcome measures; description of nimodipine's dose-regimen and confirmation of angiographic vasospasm. Studies' characteristics are presented in summary tables.

2.3. Statistical analyses

We calculated the pooled estimate of the risk ratio (RR) of cases compared with controls, using a random effects *meta*-analysis with the inverse variance method. The statistical heterogeneity of the studies' results was evaluated by the I^2 statistic, which indicates the percentage of total variation across studies that can be explained by true variation rather than chance. All analyses were performed in STATA version 15.0 (College Station, TX, USA).

3. Results

A total of 93 publications were selected for scrutiny. Following review a serues of publications were excluded in the bases of 39 duplicated publications, 40 non-randomised studies and 6 other studies with methodological misalignements. Such methodological limitations were: an RCT with experimental primates models [35], three RCT's using intravenous nimodipine [36–38], one RCT using topical nimodipine during surgical clipping [39] and a study with a combined intravenous and oral nimodipine regimen [40].

Eight RCTs were selected for full review as they met study inclusion criteria, representing a total of 1,456 patients covering the three outcome meassures. The flow of study identification and selection is displayed in Fig. 1. A description of all included studies is shown in Table 1.

The analysis of the primary endpoint (reduction in DCI events *only* related to confirmed angiographic vasospasm) included three RCTs (Table 2). A pooled RR, showed a significant reduction in the risk of angiographic vasospasm related death or vegetative state for patients taking the drug compared to placebo (pooled RR: 0.54; [95 % CI: 0.33, 0.90]), with little variation in study findings due to heterogeneity ($I^2 <$ 0.0 %, p = 0.557) (Fig. 2).

The analysis of the secondary outcome measure (the incidence of infarcts *only* related to angiographic vasospasm) revealed that one study [16] from all analysed studies, had distinguished "infarcts derived from

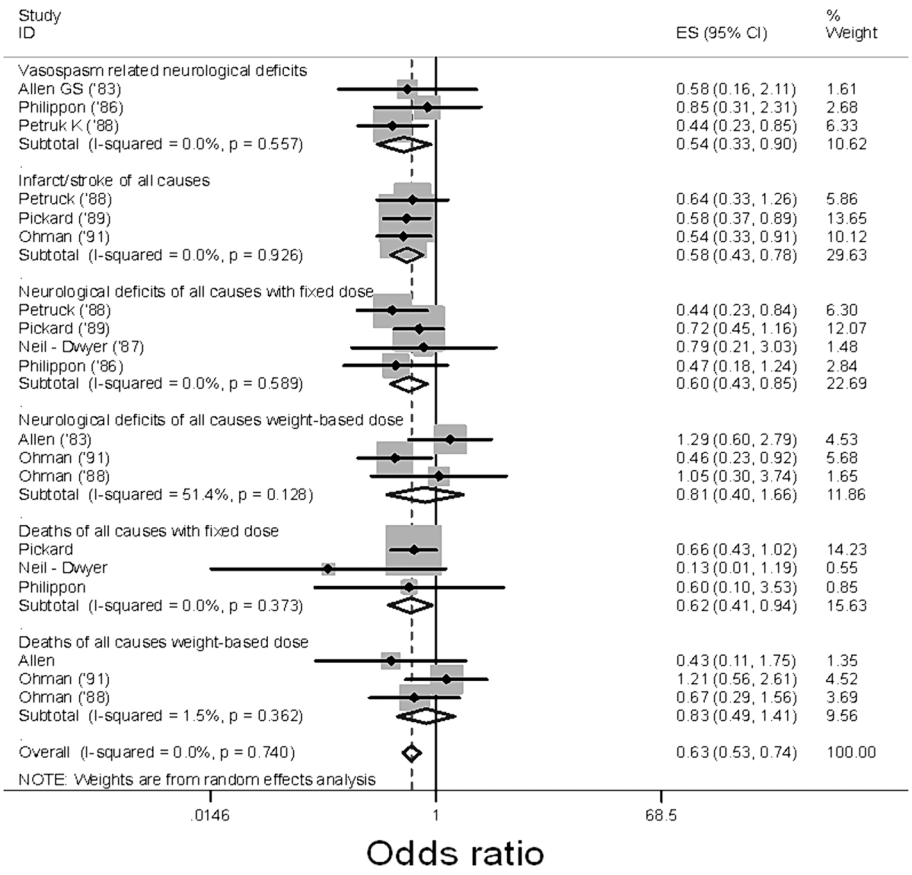
Study
ID
ES (95% CI)
%
Weight
Vasospasm related neurological deficits
Allen GS ('83) 0.58 (0.16, 2.11) 1.61
Philippon ('86) 0.85 (0.31, 2.31) 2.68
Petruk K ('88) 0.44 (0.23, 0.85) 6.33
Subtotal (I-squared = 0.0%, p = 0.557) 0.54 (0.33, 0.90) 10.62
Infarct/stroke of all causes
Petruck ('88) 0.64 (0.33, 1.26) 5.86
Pickard ('89) 0.58 (0.37, 0.89) 13.65
Ohman ('91) 0.54 (0.33, 0.91) 10.12
Subtotal (I-squared = 0.0%, p = 0.926) 0.58 (0.43, 0.78) 29.63
Neurological deficits of all causes with fixed dose
Petruck ('88) 0.44 (0.23, 0.84) 6.30
Pickard ('89) 0.72 (0.45, 1.16) 12.07
Neil - Dwyer ('87) 0.79 (0.21, 3.03) 1.48
Philippon ('86) 0.47 (0.18, 1.24) 2.84
Subtotal (I-squared = 0.0%, p = 0.589) 0.60 (0.43, 0.85) 22.69
Neurological deficits of all causes weight-based dose
Allen ('83) 1.29 (0.60, 2.79) 4.53
Ohman ('91) 0.46 (0.23, 0.92) 5.68
Ohman ('88) 1.05 (0.30, 3.74) 1.65
Subtotal (I-squared = 51.4%, p = 0.128) 0.81 (0.40, 1.66) 11.86
Deaths of all causes with fixed dose
Pickard 0.66 (0.43, 1.02) 14.23
Neil - Dwyer 0.13 (0.01, 1.19) 0.55
Philippon 0.60 (0.10, 3.53) 0.85
Subtotal (I-squared = 0.0%, p = 0.373) 0.62 (0.41, 0.94) 15.63
Deaths of all causes weight-based dose
Allen 0.43 (0.11, 1.75) 1.35
Ohman ('91) 1.21 (0.56, 2.61) 4.52
Ohman ('88) 0.67 (0.29, 1.56) 3.69
Subtotal (I-squared = 1.5%, p = 0.362) 0.83 (0.49, 1.41) 9.56
Overall (I-squared = 0.0%, p = 0.740) 0.63 (0.53, 0.74) 100.00
NOTE: Weights are from random effects analysis
.0146
1
68.5
Odds ratio

Fig. 2. Odds ratio for all studies. Odds ratio of all the selected RCT categorized by outcome measures.

confirmed angiographic vasospasm" of "infarcts of all causes" (Table 3). The pooled RR suggests that there was a significant reduction in the risk for "infarcts of all causes" for patients on nimodipine compared to placebo (pooled RR: 0.58; [95 % CI: 0.43, 0.78]), with little statistical heterogeneity ($I^2 < 0.0$ %, p = 0.926).

For the analysis of the tertiary outcome measure (a reduction on neurological deficits including deaths of *all* causes between two different nimodipine prescription regimens -a "fixed" and a "weight-based" regimen), the pooled risk ratio suggested a significant reduction in the risk for vegetative state and death for patients on nimodipine compared to placebo, more so on the fixed-dose regimen (pooled RR: 0.60; [95 % CI: 0.43, 0.85]), with little statistical heterogeneity ($I^2 < 0.0$ %, p = 0.589). Only two studies disclosed data for "cerebral infarcts of all causes" (Table 4).

4. Discussion

This scoping review examined the historical evidence for the prophylactic use of nimodipine, focusing on the reduction of DCI specific to angiographic vasospasm, a perspective without precedents [20–23]. We classified the selected RCTs according to their capacity to prevent angiographic vasospasm and influence on neurological outcomes or in studies that reported neurological deficits of any etiology. We also categorized studies upon the dose-regimen of nimodipine that was used.

Our main finding aligns with the adopted consensus that the prophylactic use of nimodipine significantly reduces the incidence of severe neurological deficits (*defined as vegetative state or death*) related to angiographic vasospasm, with no outcome benefit on lesser degrees of disability. However, it is debateable that such marginal benefit would be acceptable in contemporaneous practice. Furthermore, this outcome benefit was only shown in three [13,16,18] of all included studies, encompassing 349 subjects in total, as shown in Table 1. With such a limited cohort, the statistical significance supported by these three trials is argueable. These trials had well formulated endpoints and a robust methodology; but their individual sample size would be deemed insufficient in current practice. In Allen's study, 1 patient was affected of severe disability in the nimodipine group versus 8 patients in the placebo group; in Phillipon's study, 2 patients suferered severe disability versus 10 patients in the placebo group; in Petruck's study, 10 patients developed severe disability in the nimodipine group versus 22 patients in the placebo group. Whilst these findings are consistant, contemporaneous standards would require larger samples, specifically for pharmacological trials designed to demonstrate an outcome difference. These findings represent the example of how statistical significance may be at times of relative clinical significance. Our review questions the clinical significance of the original evidence on the prophylactic use of nimodipine, whilst suggesting that larger multiplatform trials could fine-tune the use of prophylactic nimodipine; specifically, through individualized dosing and the identification of eligible sub-cohorts of patients who may benefit the most.

Assessing the prophylactic efficacy of nimodipine against angiographic vasospasm related DCI or infarct, requires the comfirmation of a new vessel narrowing in the corresponding vascular territory; however, this level of evidence is either lacking or scarcely reported [13,16,18]. In Allen's study [13] statistical significant differences were found only for severe disability related to angiographic vasospasm; where "severe" was defined as a GCS of < 8, a marginal benefit that questions the overall role of nimodipine. Similarly, in Philippon' s [18] and Petruk's studies [16], only "severe" neurological outcomes showed a statistically significant benefit on reduced cohorts of ten and twenty-six patients respectively, but the definition of severity was not disclosed. It is unclear why nimodipine has shown benefit amongst worst outcomes although it is pathophysiologically plausible that in severe cases, the presence of diffuse cerebral ischemia could play a bigger role than regional

Table 3
Cerebral infarction of all causes amongst groups.

Author	Drug No vasospasmNo Cerebral infarction	Drug No vasospasmwith Cerebral infarction	Drug vasospasm NoCerebral infarction	Drug vasospasmwith Cerebral infarction	**Drug Infarct of all causes**	Placebo No vasospasmNo Cerebral infarction	Placebo No vasospasmwith Cerebral infarction	Placebo vasospasmNo Cerebral infarction	Placebo vasospasmwith Cerebral infarction	**Placebo Infarct of all causes**
Petruck ('88)	Not disclosed (Total of 72n on drug)	7n / 72	12n / 72	**14n / 72**	**21n / 72**	Not disclosed (Total of 82n on placebo)	8n / 82	13n / 82	**24n / 82**	**32n / 82**
Pickard ('89)	Not disclosed (Total of 278n on drug)	Not disclosed	Not disclosed	Not disclosed	**39n / 278**	Not disclosed (Total of 276n on placebo)	Not disclosed	Not disclosed	Not disclosed	**61n / 276**
Ohman ('91)	Not disclosed (Total of 104n on drug)	Not disclosed	Not disclosed	Not disclosed	**34n / 104**	Not disclosed (Total of 161n on placebo)	Not disclosed	Not disclosed	Not disclosed	**76n / 161**

angiographic vasospasm and that nimodipine's antagonizing intracellular influx of calcium could be an important determinant [41]. The primary endpoint of our scoping review aligns with the findings of those three RCT, but the overall small cohorts in those trials raise the question of *statistical* versus *clinical* significance, warranting future powered studies.

This scoping review also shows that there is not enough data to establish the prophylactic benefit of nimodipine for angiographic vasospasm related stroke. We categorized all RCTs [13–19] according to their capacity to confirm the presence of angiographic vasospasm in the anatomical region leading to an infarct as opposed to infarcts of all causes (Table 2). Three RCTs [15–17] reported stroke but only one [16] of these identified angiographic vasospasm as an attributable cause. Our pooled risk ratios show that nimodipine reduces the risk of *infarct of all causes* with substantial heterogeneity in the results. We hypothesize that the beneficial effect of nimodipine could be an epiphenomenon with DCI independent of angiographic vasospasm, as the main contributor. Therefore, the evidence that nimodipine has a prophylactic role in angiographic vasospasm related stroke is lacking.

Finally, this scoping review assessed the prophylactic effect of nimodipine between two different dose regimens. Cohort A corresponded to studies using a *fixed dose* of 60 mg nimodipine every 4 h [16–19]. Cohort B corresponded to studies with a *weight-adjusted* dose [13–15], as shown in Table 4. The pooled risk ratios for neurological deficits and death between each dose-regimen and placebo favored a fixed-dose regimen. However, in these studies neurological complications and death were multifactorial and not specifically related to angiographic vasospasm, suggesting that the benefit effect of nimodipine could have been an epiphenomenon. In addition, these studies excluded patients with renal or liver insufficiency, which contrasts with contemporaneous practice. Currently, a fixed-dose regimen to patients independent of their weight, renal or liver clearance, lacks of pharmacological reasoning and supports the need for studies that evaluate individualized dosing.

It is plausible that individualizing the dose of nimodipine, could maximise its beneficial effects whilst minimising side effects derived from overdosing, specially in patients with renal or liver dysphunction. Future studies may consider the delivery of dose-adjusting regimens, with the view of matching specific cohorts of patients to individualised dose regimens to optimize its effects.

This scoping review differs from previous reviews. We grouped the selected RCT's according to how the authors had achieved their outcome measures and noted their substantial methodological heterogeneity.

Five previous *meta*-analyses have pooled all clinical outcomes regardless their etiology and categorized it's severity utilizing a dichotomic scale of *poor* versus *not-poor* outcome. By doing so, the benefit of nimodipine could have been overrated. In the first *meta*-analysis [20] the authors included patients with preexisting angiographic vasospasm as opposed to *de-novo,* limiting the capacity to assess the prophylactic benefit of nimodipine [42]. The second *meta*-analysis [43] included non-randomized studies [44] and a study [45] utilizing xenon as opposed to angiography for the diagnosis of angiographic vasospasm, limiting their comparability. The authors noted that the majority of the analyzed trials did not have statistically significant results and they considered "*good outcome*" a Glasgow Outcome Scale of 3 or more (*anything but death and vegetative state*), an argueable definition of positive outcome.

In the third *meta*-analysis [46] the authors included a study utilizing AT877 (a calcium antagonist) [47] and a study using nicardipine [48]. Neurological outcome was categorized as "*good*" for anything except death or dependency. The authors declared that the risk reduction for vasospasm was less clear for nimodipine, however they supported the use of nimodipine whilst acknowledging that its mechanism of action is unclear.

In the fourth *meta*-analysis [49], the authors also compiled studies using any type of calcium channel blocker or magnesium and only 6

Table 4
Neurological deficits of all causes, cerebral infarcts and death between cohort A (patients with a fixed-dose regimen of nimodipine) and Cohort B (patients with a weight-based regimen of nimodipine).

Authors	**Drug Neurological deficit**	Drug CerebralInfarcts	**Drug Death**	**Placebo Neurological deficit**	PlaceboCerebral Infarct	**Placebo deaths**
Cohort A (fixed dose)						
Petruck(88)	33n / 72	21n / 72	Not disclosed	54n / 82	32n / 82	
Pickard(89)	**36n / 278**	39n / 278	**43n / 278**	**47n / 276**	61n / 276	**60n / 276**
Neil – Dwyer(87)	**5n / 25**	Not disclosed	**1n / 25**	**6n / 25**	Not disclosed	**6n / 25**
Philippon(86)	21n / 31	Not disclosed	**2n / 31**	26n / 39	Not disclosed	**4n / 39**
Cohort B (weight-based regimen)						
Allen(83)	**23n / 56**	Not disclosed	**1n / 56**	**23n / 60**	Not disclosed	**3n / 60**
Ohman ('91)	13n / 104	10n / 104	**13n / 104**	38n / 161	76n / 161	17n / 161
Ohman ('88)	**5n / 104**	Not disclosed	**1n / 104**	**5n / 109**	Not disclosed	**8n / 109**

studies exclusively used nimodipine. The authors concluded that "calcium antagonists" (*not specifically nimodipine*) reduce the risk of poor outcome and whilst they acknowledge that the evidence of nimodipine "is not beyond all doubt", they recommended its use.

In the fifth *meta*-analysis [50] the authors included studies based on prophylactic nimodipine but also studies using intra-arterial nimodipine for the treatment of established angiographic vasospasm; therefore it is not specific to the prophylactic effect of nimodipine.

The findings of this scoping review alignes with the equipoise amongst clinicians. Although it appears that the role of nimodipine is debated amongst intensivists and neurosurgeons, its administration continues to be unquestionable. In addition, the apparent harmless effects of nimodipine have been used to justify the perpetuation of a practice that would benefit revision.

Clinical practice would only be revised if supported by a new set of evidence. Future studies would have to incorporate the following considerations: if the hypothesis was that nimodipine reduces DCI related to angiographic vasospasm, the latter would have to be confirmed; new trials would have to use non-dichotomized and granular outcome data; future studies should randomize *fixed-dose* regimens versus *weight-based* dosing to explore the potential benefits of individualized dosing; finally, studies incorporating pharmacokinetic analysis could contribute to describe nimodipine's optimal dosing.

5. Conclusions

This scoping review shows that the use of nimodipine only reduces the risk of death and vegetative state related to angiographic vasospasm and the risk of stroke of all causes with a preferential effect on fixed dose regimens. The generalized use of nimodipine after SAH warrants revision. New clinical trials should be designed with a contemporaneous management and a more granular neurological outcome grading as clinical endpoints. Future studies would also benefit of applying therapeutic drug monitoring to allow for individualized dosing with the view of describing those cohorts of patients who may benefit the most.

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Judith Bellapart: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Writing – original draft. **Kevin B. Laupland:** Funding acquisition, Visualization, Writing – original draft. **Eva Malacova:** Formal analysis, Funding acquisition, Resources. **Jason A. Roberts:** Funding acquisition, Writing – review & editing. **Jennifer Paratz:** Data curation, Funding acquisition, Supervision, Visualization, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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